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A Comparison of Human Chorionic Gonadotropin with Magnesium Sulphate in Inhibition of Preterm Labor

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This study was carried out to compare the capability of HCG versus magnesium sulfate ($MgSO_4$) to inhibit preterm delivery in human cases. The study group included 101 women at 22-35 weeks of gestation with intact membranes and cervical dilatation less than 4cm in preterm labor in referrals of Obstetric-Clinic in the city of Khoram Abad during the year 2001-2003. The cases and control groups were treated with HCG protocol of the dosage consisting of one single dose of HCG 5000 1 V and 10000 units of HCG in 500 dextrose as a drip of 20 drops per minute and magnesium sulfute (Rotin dose), respectively and treated until preterm labor (PTL) arrested. Complications were recorded. On condition of successful cease of labor, the patients were discharged and followed up to the time of delivery. Both group were similar to each other regarding maternal age, parity and gestational age. Delivery was delayed for 48 h in 45(90.3%) and 44(88%) of the patients in the HCG and magnesium sulfate groups. The number of newborns that were admitted to NICU was 9 (18%) for HCG and $MgSO_4$. In addition, mean weight at labor was 2334 and 2287 g for HCG and $MgSO_4$. The complaint rate was 100 and 0% for magnesium sulfate and HCG group, respectively ($p<0.0001$). Since both drugs are alike regarding their effects on birth time weight and delay of labor and in addition HCG exhibits without fetal side effects. So it is recommended to be used in prevention of preterm labor replacement of $MgSO_4$.

Key words: Preterm labor, HCG, magnesium sulfate

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INTRODUCTION

Preterm labor and delivery continue to occupy the obstetrical research community because of the public health problem they continue to generate. Existing therapies for preterm labor at best delay delivery for 48 h, during which time glucocorticoids can be given to enhance fetal lung maturity and so reduce the likelihood or severity of respiratory distress syndrome; intraventricular haemorrhage, necrotising enterocolitis, neonatal death and length of neonatal hospital stay (Lockwood, 1997).

Now there are no agreed protocols for the management of preterm labor and the management of preterm labor remains contentious (Savvidou *et al*., 1998). So, physicians must diagnose and mange preterm labor amid substantial controversy over the effectiveness of preventive and therapeutic modalities (Edward *et al*., 2004; Goldenberg *et al*., 2002). Corticosteroids, tocolytics and to some extent antibiotics have all been shown to have a role to play in the management.

Magnesium sulphate has been used as a tocolytic in American obstetric practice since the 1960 (Bennet and Edward, 1997). Also it is routinely used in our country as a tocolytic agent. The evidence that supports its use for tocolysis is weak. Magnesium ions do inhibit myometrial contractility *in vitro*, probably by inhibition of myometrial calcium channels. However randomized trials show that it is no better than placebo at delaying preterm delivery (Witlin *et al*., 1997; Mcwhorter, 2004). Complications associated with the use of magnesium sulfate include nausea, vomiting, hypotension, headache and the more severe effects of respiratory depression and pulmonary edema. Because magnesium sulfate crosses the placenta, fetal side effects include decreased muscle tone and lethargy (Adrienne *et al*., 2005).

Previous work has demonstrated that luteinizing hormone (L-H) -Human Chorionic Gonadotropin (HCG) receptors are present in numerous nongonadal tissues, including human myometrium (Reshef *et al*., 1990; Al-Hadar *et al*., 1998; Ambrus and Rao, 1998; Lei *et al*., 1994).

Additionally, LH-HCG myometrial receptor down-regulation accompanies labor in term, as well as preterm, gestations (Zuo *et al*., 1994). In isolated strips of human myometrium, the addition of HCG decreases the amplitude of myometrial contractions). When administered in early pregnancy, HCG decreases resistance of blood flow in the uterine artery (Toth *et al*., 1998).

On the basis of these studies we hypothesized that HCG may play a physiologic role in the maintenance of uterine quiescence. As such, HCG may be capable of inhibiting preterm delivery in human. So, in this study we decided to compare the tocolytic effect and probable complications of HCG and Magnesium sulphate.

MATERIALS AND METHODS

This study was designed as a randomized clinical trial. From February 2000 to February 2002, pregnant women with pretem labor, who were admitted to Khorram Abad hospitals, in the west of Iran, were invited to participate. One hundred and one cases who consented were randomly allocated to 2 different intervention groups, named A and B. Group A and B consisted of 50 and 51 pregnant women, respectively.

A diagnosis of preterm labor was made in patients between 20 weeks and 36 weeks, six days of gestation if uterine contractions at a frequency of four per 20 min or eight per 60 min and were accompanied by one of the following: premature rupture of membrane, cervical dilation greater than 2 cm, effacement exceeding 50% , or a change in cervical dilation or effacement detected by serial examinations. The patients placed in the lateral recumbent position and externally monitored for fetal heart tones and contractions. If uterine contractions were present at least every 15 min, an intravenous bolus of 500 mL of normal saline was administered. This rapid intravascular expansion can diminish the contractions of an irritable uterus and help the physician differentiate this condition from preterm labor. By this method patients could be included.

Exclusion criteria were premature rupture of membrane, cervical dilatation more than 4 cm placental abruption diabetes mellitus, cardiorespiratory diseases, genitourinary infections, anatomical anomalies of the pelvis and fetal anomalies.

For patients of group A, intravenous HCG was administered in an initial dose of 5000 IU.

Then 10000 IU of HCG in 500 mL of D5W was administered by the order of 20 drops per minute intravenously. The protocol was continued until the time that contractions discontinued.

Patients of group B received a loading dose of 4 g intravenously (1 g/min) Magnesium sulphate. A continuous infusion of 2 g h^{-1} was then administrated. The infusion was continued until 12 h of uterine quiescence is achieved. In both groups, if contractions continued by previous or a higher force and frequency, or dilatation progressed the patient was excluded and management of patient was continued out of the study protocols. So patients could be switched to another tocolytic regimen if they continued to have contractions after 6 h of therapy.

All of the patients were under observe in the hospital until 24 h of the end of drug infusion. Also, both of the groups received dexamethasone, 5 mg bid for 4 doses. Patients were under control until the end of pregnancy.

In this study data such as maternal. gestational age when the diagnosis of perterm labor was achieved, delay of labor due to treatment protocols, frequency of complications in both groups were registered.

Data were collected using questioners and clinical examination. Results were analyzed using descriptive statistics, distributional indices. Independent t-test was occupied to compare maternal age, gravidity, time of admission and neonatal birth weight between two groups.

RESULTS

Both groups were similar to each other regarding maternal age and gestational age (Table 1). The only multiple gestations enrolled were twins and 4 patients in each group had a twin gestation. The incidence of success was similar between the groups at 37(74%) and 36 (73%), HCG and magnesium sulphate. Delivery was delayed 48 h in 45(90.3%) and 44(88%) patients in the HCG and magnesium sulphate groups (Table 2).

There was not any complication in group A and all of the patients in group B had complications such as thirst, flashing, headache, vertigo, nausea and vomiting (Table 3). NO sever complication was detected during the study. There was no significant difference between the outcomes between study groups (Table 2).

The mean of neonatal birth weight in group A was 2334±631.03. This mean for group B was 2287.25±498.7. There parameters were not statistically different (p-value = 0.68).

Table 1: Demographic characteristics

Duration	Magnesium sulphate	HCG
Maternal age	24.50	24.30
Parity	2.12	1.98
Onset of pain (week)	31.34	31.59
End of pain (week)	34.85	34.83
Mean weight (g)	2287.25	2234.00

Table 2: The comparison of tocolytic function and outcomes in the groups

Mean delay of labor	Mean (48 h)
Magnesium sulphate	44 (88%)
HCG	45 (90.3%)

Table 3: The frequency of complications in HCG and Magnesium sulphate intervention groups

Diseases	HCG (n = 50)	Magnesium sulphate (n = 51)
Headache	0	19 (37.25%)
Vertigo	0	4 (7.84%)
Nausea and vomiting	0	32 (62.70%)
Flushing	0	51 (100.00%)
Nausea and headache	0	24 (47.06%)
Flashing and nausea and Headache	0	

There was not any perinatal mortality in the two groups. In each of study groups 9(0.18% in group A and 17.65% in group B) neonates were admitted to NICU, due to respiratory distress. All of the neonates and mothers were discharged by a stable position and with no problem.

DISCUSSION

Human myometrium contain HCG/lh receptors. There are fewer of these receptors during labor compared to no labor at preterm or term deliveries. Exogenous HCG can directly inhibit oxytocin-stimulated human myometrial contraction (Ambrus and Rao, 1998). These finding suggest that HCG may directly maintain myometrial quiescence during pregnancy (Eta *et al*., 1994; Toppozada *et al*., 1998). As maintenance of uterine quiescence may involve down-regulation of myometrial gap junctions, we investigated the effect of HCG on connexin 43 (cx-43) gene expression from RNA to protein and morphological gap junctions (Ambrus and Rao, 1998). Present results demonstrated that HCG could be one of the hormones responsible for maintaining uterine quiescence by down-regulating myometrial gap junctions during pregnancy. The HCG action is concentration and time dependent, hormone special and mediated by protein kinase-A signaling and appears to involve progesterone receptors (Kurtzman *et al*., 1999). We choose magnesium sulphate as the control drug because it is our first-line tocolytic. Although the overall efficacy of magnesium sulphate as a tocolytic is arguable (Edward *et al*., 2004; Canadian Preterm Labor Group, 1992). It has been used for more than 3 decades. The frequency of maternal side effects has been a consistent concern and it appears that the margin between maternal safety and efficacy of magnesium sulphate infusion for tocolysis is quite narrow (Atkinson *et al*., 1995). We likewise noted a high incidence of maternal side effects (100%) and no dis continuation rate in the magnesium sulphate group. This is consistent with an earlier study (Bennet, 1997) showing a 10% discontinuation rate in patients treated with magnesium sulphate infusion for tocolysis with an overall 31% incidence of reported side effects (Macwhorter-Edward 2004). In Behnam (2001) study an overall 100% incidence of reported side effects. Despite the encouraging results of recent studies (Adrienne *et al*., 2005; Kornyei *et al*., 2003) demonstrating improved methods of predict prematurity and prevent preterm labor, the incidence of preterm delivery has remained stable during the last 20 years (Adrienne *et al*., 2005) clearly new methods to arrest acute preterm labor are needed. HCG is a new drug that inhibit human myometrial contractions. The ability of HCG to inhibit preterm delivery may be

mediated further by directly suppressing myometrial responsiveness to stimulatory eicosanoids (Zuo *et al*., 1994b). HCG-may also increase the formation of eicosanoids that prompt myometrial relaxation, such as prostacyclin (Swanson *et al*., 1992; Toth and Rao, 1994) In the present study demonstrated that HCG comparable clinical efficacy in delaying delivery for 48 h in direct comparison with magnesium sulphate. Our study may have two limitations and could be improved in several ways. First we may have over diagnosed preterm labor and treated some women in both groups un necessarily. When preterm labor in diagnosed on the basis of contraction alone, between 30 and 70% of women will resolve without treatment. In this circumstance many more patients would be required to determine a benefit of HCG. It is likely that, despite the entry criteria, many of our patients were not in true groups is the result of our definition of preterm labor. Second, we did not exclude twins in our study. The dynamics of premature uterine contractions in twins may be different from those in singleton pregnancies, because of uterine over distension, but strict entry criteria and the blind randomization process should have eliminated of bias. In addition, there was no difference in the number of twins in each randomized group. Accumulating data suggest that prolonged tocolytic treatment is not effective in improving neonatal outcome and remains controversial. There is a strong consensus, however that in those patients who present with active labor before 34 weeks of gestation that a 48 h delay in delivery until a full course of dexamethasone is completed, will have improved neonatal outcomes (Savvidou *et al*., 1998).

CONCLUSIONS

This study suggests that HCG may be a therapeutic candidate for inhibition of preterm labor in human pregnancy, due to its effectiveness and not prominent demonstrated complications. Further work is needed to delineate the mechanism of action, as well as the safety and efficacy of HCG for use in the prevention of human preterm delivery. In order to find the most effective dose of, HCG further studies are suggested.

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